THE CORONARY HEMODYNAMIC RESPONSE TO ENVIRONMENT

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AEROSPACE MEDICAL LABORATORY
AERONAUTICAL SYSTEMS DIVISION
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FOREWORD

This report was prepared in support of Project No. 7163, "Physiology Research," and Task No. 716302, "Vital Organ Function Studies in Mammals." The work was performed under Contract No. AF 33(616)-6928, administered by the Respiration Section, Physiology Branch, Biomedical Laboratory, Aerospace Medical Laboratory, Aeronautical Systems Division, Wright-Patterson Air Force Base, Ohio, with Mr. Donald A. Rosenbaum serving as contract monitor. The work was performed by Dr. Eric Ogden, Dr. Heinz Pieper, Dr. Leo A. Sapirstein, and Miss Phyllis Arscott.

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The experiments reported herein were conducted according to the "Rules Regarding Animal Care" established by the American Medical Association.

ABSTRACT

Positive pressure breathing with 100 percent oxygen in dogs wearing bladder-type partial pressure suits causes major reduction in the cardiac output despite equal counter pressure to the respiratory passageway and the absence of pulmonary hyperinflation. These experiments were carried out to investigate the possibility that the circulatory defect was a consequence of defective myocardial perfusion. The experimental work revealed that coronary blood flow was significantly reduced in dogs wearing the pressure suit. The reduction in coronary flow was insignificantly less than the reduction in cardiac output and the coronary resistance was increased. This is in contrast with what is observed when the primary circulatory defect is one of the failure of venous return. This suggests that the major circulatory difficulty encountered in the pressure suit used may be a consequence of coronary vasoconstriction as a primary event. The circulatory failure which occurs in the pressure suit may be of cardiac rather than peripheral origin.

PUBLICATION REVIEW

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SECTION I. HISTORICAL INTRODUCTION

The use of pressure suits to counteract the adverse effects of sudden or chronic exposure to low barometric pressure is of obvious importance in circumstances where men may be separated from an environment of very low pressure by an enclosure which is subject to mechanical failure. In effect, the pressure suit should serve to decrease the probability that accidents may lead to exposure to such pressures by acting as a cabin within a cabin, the smaller cabin, being of approximately the size and shape of the man.

Various types of suits have been devised. One type of considerable importance consists of a Nylon suit somewhat larger than the man. The space between the suit and the torso of the subject is occupied by inflatable bladders; the extremities are closely enveloped by the fabric, and the pressure exerted by the fabric upon them is varied by the inflation of a longitudinal bladder whose radial expansion increases the tension exerted by the fabric on the contents. The external pressures produced by the inflation of the bladders upon the torso and the extremities are, in turn, countered by the application of an equal pressure to the airway through the rigid helmet which envelops the head. Such suits are in current use in the United States Air Force.

For certain physiological studies on the effects of pressure suits, it was necessary to develop a suit with similar properties which could be applied to the ordinary laboratory animals. Such a suit, applicable to the dog, was designed and extensively studied at the Wright-Patterson Air Force Base. Other studies on this suit were carried out by Williams and Horvath at the State University of Iowa,[1] and Carter, Reininger and Hitchcock at The Ohio State University.[2]

In some of these studies it became apparent that the suit which had been developed for the dog had adverse circulatory effects. Among these were: reduction in circulating blood volume, reduction in arterial pressure and reduction in the cardiac output. It has been suggested[1] that these effects are essentially those of positive pressure breathing inadequately compensated by external pressure.

From their studies Williams and Horvath concluded that the pressure suit used on dogs failed to provide complete and prolonged protection. Carter and Hitchcok (1959) concluded from a limited number of cardiovascular measurements on dogs wearing the pressure suit that "it is improbable that any partial pressure suit will ever be completely satisfactory." Since the cause of the disturbance in cardiovascular function was not identified, this conclusion may be regarded as perhaps premature.

The present investigations were begun in an attempt to characterize further the basic disturbances responsible for cardiovascular malfunction in the pressure suit. It had been suggested among other possibilities that unequal application of counterpressure to the body of the dog might result in redistributions of blood volume within the animal of such nature as to excite volume receptors within the thorax, whose effect might be to induce coronary vasoconstriction and a consequent myocardial insufficiency. It was, therefore, of interest to determine the effects of the suit on coronary blood flow.

This report describes the results of our measurements of coronary blood flow and a number of other circulatory parameters in dogs wearing pressure suits. The results are compatible with the view that the primary circulatory defect may be a consequence of a coronary vasoconstriction rather than of peripheral circulatory origin.

SECTION II. TECHNIQUES

A. PREPARATION AND SELECTION OF DOGS

1. Selection and Preexperimental Regime

The pressure suits which were available to us for these studies were suitable for dogs weighing from 9-13 kilograms. In general, for the suit to fit properly the animals had to be narrow chested. Most of the animals had been acquired within two or three days of use; some animals had been in the laboratory for several months. There was no detectable difference in the results of the two groups.

Before use, the animals were fasted for 24 hours. Free access to water was allowed during the fast.

2. Anesthesia

Despite the advantages of chloralose anesthesia in the preservation of cardiovascular reflexes, the conveniences of sodium pentobarbital anesthesia so far outweighed them, that the latter was the anesthetic used. The dose was 30 mg. per kilo given by the intravenous route. In those experiments, which were of long enough duration to require additional anesthesia, further administration of the pentobarbital was made by the intravenous route, the administered dose being determined by the effect on the animal.

3. Surgical Procedures

a. Placement of catheters--Two techniques were used for catheter placement. In some experiments a thin-walled No. 17 Cournand needle was introduced into the vessel to be catheterized, a polyethylene tube threaded through the needle into the vessel and the needle then removed while the catheter remained in the vessel. To guard against inadvertent withdrawal of the catheter during subsequent manipulations it was tied into a loose square knot which was anchored by two skin sutures. In general, this technique was suitable for venous cannulation but was not entirely adequate for arterial cannulation. In many experiments, therefore, both venous and arterial catheterization were accomplished by direct cut-down.

b. Splenectomy--In a number of experiments, splenectomized dogs were used. The splenectomy was accomplished under sodium-pentobarbital anesthesia at least 2 weeks prior to the experiment.

B. APPLICATION OF THE SUIT

The suit has been described elsewhere and a photograph is available in Williams and Horvath report, 1959, Fig. 1.[1] The suit is so designed that repeated longitudinal lacings appear to be necessary for each application. Indeed, insofar as the fit of the suit is concerned, it is advisable since improper alignment might lead to wrinkling and consequent drag or strain upon the fabric of the suit, especially after inflation. This situation could easily create unequal tensions upon the animals surface. This is the case, however, only if animals weighing outside the 9-13 kilogram range are used. We chose to take advantage of the fact that dogs within the stipulated range were easily accommodated by either one or the other of the two sizes of suits provided, and thus needed no further size adjustment. This meant that an initial, even lacing was sufficient. Following catheterization, the anesthetized dog was placed in a supine position on a dog board preparatory to applying the suit. The holes which accommodated the lower extremities were dropped over the hind legs first; the upper portion of the suit was drawn up over the chest and the front paws inserted individually into the holes for the upper extremities. The suit containing the dog was then grasped on either side of its rear zipper closure and lifted from the table with the dog slung in a prone position. Two or three shaking maneuvers served to adjust the suit to the animal so that the zipper could be closed easily. The dog was then returned to its original supine position. Following this, the neck piece was applied. Previously the neck had been shaved closely so that the rubber insert of the neck piece would adhere closely to the neck of the dog. After the neckpiece was in place, and before closing its rear zipper closure, approximately 1 inch of the rubber insert was turned cephalad.

The bladder suit was inflated to the desired pressure by throwing a lever which permitted gas under pressure to enter it through a hose which led into the bladder at the lateral aspect of the suit. On the opposite side of the suit a second hose made a connection between the suit and the helmet. In this manner, since a discontinuity existed at the neck between the helmet and the suit, equal pressure was applied to the body and the head, and thus to the airways as well. Standard pressure breathing valves made respiration possible. Once equal pressures existed between bladder and helmet, the inspiratory valve located in the helmet opened only during the inspiratory phase of respiration. Subsequently it closed at the beginning of expiration when the second valve, located in the helmet wall opened, permitting expulsion to the outside of that quantity of air expired.

Pressures of either 100 or 200 mm of Hg were used for all experiments. Under these conditions a certain amount of leakage of gas occurred, especially at the suit seams or at the sleeve edges where the bladder tapered off. This was compensated for by the nature of the gas supply. The suit used for the majority of these experiments was of the type which did not enclose the legs of the animal. Two other suits were made available at different times during the course of the study. One covered the legs, excluding the paws only, while another completely encompassed the whole leg. The gas used in all cases was 100 percent oxygen. All experiments were done at ground level.

C. MEASUREMENT OF THE CARDIAC OUTPUT

The cardiac output was measured in these experiments by the Stewart-Hamilton technique using T 1824 (Evans Blue) or $Rb^{86}Cl$ as the indicator. In preliminary experiments attempts were made to measure the cardiac output with autogenous plasma using the resistance of the blood as the indicator measurement according to the technique of Goodwin and Sapirstein[3]. For reasons which are, at the moment, not clear, this technique fails to yield useable results in the experimental circumstances, and consequently the classical dye techniques were employed.

After the nearly instantaneous injection of 20 mg. of dye or 10-20 microcuries of Rb^{86} by way of the femoral venous catheter, blood samples were collected through the femoral arterial catheter which delivered into a collecting disk of the type described by Rothe and Sapirstein[4]. The collection rate was adjusted to be between 30-40 samples per minute. At this collection rate, and with the cardiac outputs encountered, the dilution curve could be constructed with at least four blood samples describing the downslope.

The calculation of the cardiac output was accomplished as follows. When Evans Blue was used, the optical density of the injected dose, suitably diluted, was multiplied by the dilution factor and the observed rate of sample collection (number of samples per minute). This product was divided by the sum of the optical densities of the samples up to the moment of recirculation, identified as the breakaway from linearity on a semilogarithmic plot of concentration versus time; to which was added the sum, extrapolated to infinity, of the exponential decay of the descending points. It has been pointed out, that the extrapolation involved in the dye dilution method is only approximate. Nevertheless, for the accuracy required in these experiments, and in view of the known variability of the cardiac output, the assumptions made in the calculation according to the Stewart-Hamilton method seem sufficiently valid to justify the use of their equation. When Rb^{86} was the indicator the determination of label concentration in the blood samples was made by counting an aliquot rather than by colorimetry; the procedure and calculations were otherwise the same.

D. MEASUREMENT OF REGIONAL BLOOD FLOW DISTRIBUTION

1. The Principle of the Method

The method used in the determination of regional blood flow in these experiments is essentially a modification of the Fick principle as modified by Kety and Schmidt[5], and as further modified by Sapirstein et al[6-9].

Basically the method depends upon the fact that any organ content of any indicator can be described as the product of the blood flow to that organ and the difference between the integrated arterial and integrated venous concentration of that indicator.

Whenever it is the case that the venous concentration is negligibly small with respect to the arterial concentration of indicator, then clearly it becomes possible to describe the amount of indicator in an organ as the product of organ blood flow and integrated arterial concentration.

To illustrate this concept we may consider the behavior of glass beads larger than capillaries after injection into the left heart. Self-evidently, these beads will act as labels for the arterial blood; on the other hand, they will not act as labels for the venous blood since they have been entirely lost in the capillaries. Their venous concentration is consequently zero; their total delivery to the organ depends on blood flow and arterial concentration. If every organ behaves in this manner then the cardiac output may be described as the ratio between the number of beads injected and their integrated arterial concentration. The blood flow to any organ may likewise be described as the ratio between the amount of beads found in that organ and the integrated arterial concentration of beads. From these statements, it follows that the ratio of organ circulation to cardiac output may be described as the ratio between the number of beads found in the organ and the number of beads injected.

Of course, one must raise the question whether it is genuinely the case that the beads have been completely trapped in the capillaries, since the possibility exists that some of them may have gradually worked their way through these vessels. But here, we may impose a new condition; we will recognize the failure of trapping by observing that the number of beads in any organ changes as a function of time. Those organs which are most effective at trapping beads will progressively gain from the circulation beads which have been lost from those organs which are ineffective at trapping them; these latter in turn will progressively lose beads as a function of time.

If the situation should ever be observed where the number of beads in all organs remains fixed over a long period of time, then it could be concluded that all organs had completely trapped all the beads which had arrived to them by way of their arterial blood supply and in this situation the partition of the beads among the organs would correspond to the partition of the cardiac output among them.

This proposition, that the distribution of a label corresponds to the distribution of the cardiac output, provided that the former does not change significantly with time over a significant time period beginning with the moment of initial delivery, is valid no matter what the mechanism of label trapping may be. In the case of beads, the trapping is mechanical, but chemical or exchange capture would lead to precisely the same results.

The widest application of this principle for blood flow measurement has been in connection with an indicator which is captured by exchange (K^{42}). More recently, Rb^{86} has been found to display the same behavior and has, for most purposes, replaced K^{42} in the application of the principle. It is beyond the scope of the present discussion to consider why these indicators are suitable; a discussion of the reasons for their behavior may be found elsewhere[7].

2. Practice of the Method

In practice, the determination of flow distribution was made as follows. A measured quantity (usually approximately 20 microcuries) of $Rb^{86}Cl$ was injected as rapidly as possible into the femoral venous catheter. The injection ordinarily occupied no more than 1-2 seconds. Femoral arterial blood sampling for the determination of the cardiac output was begun simultaneously with the injection. A sufficient time was allowed to permit the injected label to pass into the arterial circulation (usually 30-60 seconds) and the animal was then killed by the intravenous injection of saturated KCl.

The organs whose blood blow was to be measured were removed for counting. These were usually the heart, lungs, liver, intestine, stomach, spleen, kidneys, pancreas, and adrenal.

The organs were placed in tared beakers and weighed. The organ label content was then determined by placing the beaker containing the organ in a deep well counter, sensitive to the gamma emission of Rb^{86}. The detector used was the Nucleonic Corporation of America's WC-3 multiple bismuth tube array. The counts were displayed through a Nuclear Chicago Ultrascaler. All organ counts were compared to the counts of a standard, prepared from an aliquot fraction of the injected solution. The ratio between the counts found in the organ and the number of counts injected (obtained by multiplying the standard count by the reciprocal of the aliquot fraction) was taken as the fraction of the cardiac output which had perfused the organ.

It is important to note here that the well used in these experiments had the remarkable and very desirable property that the count rate of a sample was almost completely independent of sample volume when the sample was positioned in the center of the well. The expected self absorption of gammas in larger volumes was not noted. Not all wells appear to have this property which is, at the moment, unexplained. For example, a large plastic scintillator fashioned into a well of the same size as that used, showed a strong dependence of sample count on sample volume, unless the counter sensitivity was made so high that a background count of almost 700,000 cpm was obtained.

3. Possible Limitations of the Method

It must be emphasized at this point that the indicator fractionation technique measures only the nutritional blood supply of an organ. Blood flowing through non-exchanging channels, e.g., arteriovenous anastomoses, remains undetected. Such flow can only be detected by making large numbers of observations over very short time intervals after injection of label; arteriovenous anastomoses are then displayed by a rapid rise and fall in organ indicator content, the peak value corresponding to the location of the crest of the wave of arterial concentration in the blood vessels of the organ; the decline representing the rapid wash-out of the "unaccepted" indicator, and corresponding to the downslope of the indicator dilution curve in the arterial blood.

Another important limitation of the method is concerned with the criterion of constancy. It will be recalled that an organ which traps the label

more effectively than the body as a whole will gain label with time, and contrarily, an organ which is a poor trap will continually lose label to the rest of the body. The necessary and sufficient condition for the identity between flow fraction and label uptake fraction is constancy of the latter with time.

This condition is simply met, when the rat is the experimental animal, by dividing the animals into groups which are killed at different times after label administration. When the groups are sufficiently large, it is quite easy to determine whether or not the condition of constancy has been met. In the case of larger and less uniform animals, as the dog, it is for evident reasons, much more difficult to apply this method.

In the present experiments, we have not attempted to demonstrate the condition of constancy. However, from previous experience with both dogs and rats, and from theoretical considerations we feel justified in making the following statement: During the first minute after Rb^{86} injection, significant redistributions can occur in only two circumstances; (1) where non-exchanging channels begin to carry a significant portion of the total flow to any organ; (2) where the perfusion rate of an organ becomes much larger in relation to the reservoir of molecules available for exchange with the label than is ordinarily the case. As indicated above, the method is not intended to measure anastomotic flow, and this must be recognized in the interpretation of the results; so far as the possibility of increased perfusion rates is concerned, this does not appear to be probable in the present experiments where the cardiac output is very substantially reduced.

One further point should be emphasized. The results obtained by the indicator fractionation technique describe blood flow <u>to</u> organs and not <u>through</u> arteries. An illustration of the confusion which may develop through neglect of this is in the comparison of measurements of cerebral and carotid blood flows. The electromagnetic flow meter indicates a very slight increase in carotid blood flow after the administration of epinephrine; the indicator fractionation technique shows a very substantial increase in cerebral blood flow. The two results, which appear at first sight inconsistent, are quite compatible. The cerebral portion of the common carotid blood flow is inconsiderably small in the experimental animals which were studied (sheep); though this portion is substantially increased, the increase is very slight in relation to total common carotid blood flow. Another illustration of the same type of misinterpretation is in the application of the findings by physical methods of flow measurement through limb arteries to either muscle or skin, when these may vary in opposite directions.

E. CALCULATION OF REGIONAL BLOOD FLOW

Flow values obtained by the indicator fractionation technique are always given as fractions of the cardiac output; they can be converted to actual flows only by multiplication of the fraction by the cardiac output. In all the animals exposed to pressure the animal's own cardiac output was combined with the organ fraction to yield flow values. In the controls, however, it was often the case that output data were available without flow fractions, and vice versa. Since the values for both output and organ fractions showed

very little variability from each other, the control flow values were calculated from the group averages for output and fractional flows.

F. MEASUREMENT OF ARTERIAL PRESSURES

Arterial pressures in most experiments were measured by means of a Statham P23d Physiological Pressure Transducer used in conjunction with a Statham Strain Gauge Amplifier and a direct writing system. The gauge was calibrated against a mercury manometer before each experiment. In a few experiments intravascular manometers were used.

Mean arterial pressure was measured from the tracing either by eye or by use of the approximate formula,

$$\text{mean pressure} = \frac{2\,(\text{diastolic pressure}) + \text{systolic pressure}}{3}.$$

The two estimates invariably agreed to within 5 mm Hg.

For all calculations in which arterial pressures of dogs within the inflated suit were used, the value used was the observed arterial pressure diminished by suit pressure. Thus, if an animal was exposed to a suit pressure of 100 mm Hg and the mean arterial pressure was found to be 180 mm Hg, the pressure used for resistance calculations was 80:(180-100) mm Hg.

G. CALCULATION OF TERRITORIAL RESISTANCES

Territorial resistances were calculated as the ratio between the arterial pressure expressed in dynes/square cm and the volume flow expressed in cm^3/sec. In the case of experimental animals where all the necessary data were available for the calculation in every animal, the values were calculated on an individual basis. In the controls, where flow calculations were based on a group average, and where pressures were also calculated from the mean of the group, all such calculations represent the behavior of the group rather than of the individuals which composed it.

H. CALCULATION OF THE POWER OF THE HEART

For reasons which will become apparent later, it was, in many cases, necessary to calculate the power of the heart. Because of the use to which the calculations were put, it was felt unnecessary to use the more exact formulations for the calculation. Heart power was, therefore, calculated simply as the product of the mean arterial pressure (in dynes per square cm) and the cardiac output(in cm^3/min). Using these dimensions, the answer obtained is in ergs/min.

I. MEASUREMENT OF BLOOD VOLUME

1. Measurement of Plasma Volume

Plasma volume was determined by measuring Evans Blue dilution. Twenty milligrams of dye in 10 ml of saline was injected via femoral vein. Arterial blood samples were taken at 5 and 10 minutes after the injection. The blood was centrifuged and the plasma taken for color analysis. A standard containing the injected amount of Evans Blue diluted to 500 ml was used for the color comparison. The "standard" in its final dilution (1:4) contained as much blank plasma (1 ml) as the measured sample. This was necessary to allow for the distortion of the color produced by plasma proteins.

Plasma volume was calculated from the ratio between the optical density of the injected dye and the optical density of the plasma samples. Since the standard was made from the injected dye by diluting 1:500, the volume was calculated by multiplying the ratio between the standard optical density and that of the measured sample by 500. Although it was originally intended that the optical density of the sample at zero time should be determined by extrapolating the 5 and 10 minute values to zero time, in any individual pair of determinations the difference between the 5 and 10 minute values might be in either direction. We, therefore, chose to use the mean of the two determinations rather than to make the theoretically required extrapolation.

When determinations of blood volume were to be repeated on the same dog at short intervals, the "background" of residual dye left from the initial determination was subtracted from the values obtained in the second, etc. At first, second determinations were made with twice the initial quantity of dye to diminish the error due to the high and relatively uncertain "background." Later experience, however, proved this to be unnecessary, and 10 milligrams of dye was used for both first and second determinations.

2. Measurement of Hematocrit and Calculation of Blood Volume

The hematocrit determinations were made on the same blood samples which were used for the determination of plasma volume, usually taken from the femoral artery. Occasionally, hematocrits were measured when blood volume was not being determined; in these cases either arterial or venous blood was used. There was no detectable difference in hematocrit between venous and arterial bloods in dogs wearing the pressure suit.

The blood samples were taken up into small capillary tubes of uniform bore and immediately centrifuged in a microcentrifuge for 5 minutes. Each sample was determined at least in duplicate but in most cases in quadruplicate.

Blood volume was calculated from the plasma volume and the hematocrit by dividing the former by one minus the hematocrit.

$$B.V. = \frac{P.V.}{1\text{-hct}}$$

J. THE DESIGN AND CONSTRUCTION OF AN ORIFICE METER FOR THE MEASUREMENT OF CORONARY BLOOD FLOW

The indicator fractionation method for the measurement of regional blood flow suffers from the disadvantage that each measurement is a terminal one. When, therefore, it becomes essential to make a measurement in control and in experimental conditions, it is necessary to survey two separate populations of animals. It would clearly be advantageous to be able to make the blood flow measurement repetitively in any one animal as it passed from the control condition to the experimental one.

So far as the coronary circulation is concerned, to meet the requirement suggested above with techniques currently available would involve surgical invasion of the thorax. In circumstances where counterpressure is being applied to the thorax, such invasion carries with it the technical question whether the circumstances of interest are really being investigated.

The ideal solution to these questions would be the development of a continuous physical measurement of coronary blood flow which did not depend for its execution upon opening of the thoracic cage.

Such a solution is, in principle, available. If a flowmeter could be introduced on a catheter tip; and if the catheter could be inserted into the sinus of Valsalva via some artery external to the thorax, flow into the coronary system would be measured continuously as a function of time without interference with the normal function of the organism or the circumstances of application of the pressure suit.

Flowmeters of the type implied are, in fact, already available. One of us, (HP) has developed a catheter tip flowmeter which uses the differential transformer with variable coupling. A small ring which is connected to the ferromagnetic core of the transformer and which is axially oriented in the blood stream is displaced by the viscous drag of the passing blood. It can be shown that the displacement is linearly proportional to flow velocity, and for pulsatile turbulent flow such as would exist in a cannula adapted for the measurement of coronary flow the flowmeter has a linear characteristic and linear frequency response up to 50 cps.

The problem of establishing a mechanical connection between the flow measuring cannula and the coronary system causes considerable difficulties. It has been attempted to insert a short polyethylene catheter into the left coronary artery in such a way that it is wedged into the coronary ostium, the catheter being connected to the flow measuring cannula. In spite of many attempts, insertion has not been accomplished in the closed chest dog. It is now suggested to establish a connection between the flowmeter and the coronary system by means of a cup-shaped connection made from soft rubber. The cup may be rolled into a small cylinder in order to pass through the carotid artery and, in the wider cross-section of the aorta, it will assume its original shape large enough to cover the coronary ostium. Blood from the ascending aorta would have to enter the coronary artery by passing through the flowmeter attached to the cup. Calibration of the flowmeter would be done with the dog's

own blood using pulsatile flow of known magnitude. Preliminary experiments showed the feasibility of such an approach to the problem. However, the refinement of this method to the point where it could have been used in the present work would have unduly delayed the completion of the work. Therefore, after preliminary trial, the use of this method was discontinued.

SECTION III. FINDINGS

A. THE BEHAVIOR OF THE CARDIAC OUTPUT OF THE DOG IN THE PRESSURE SUIT

1. 100 Millimeters Positive Pressure

a. For 20 minutes--The cardiac output in the pressure suit was almost invariably decreased below the control level of animals observed in this colony, or those placed in the pressure suit without inflation. The fall was to about half the control value (54%). In the animals referred to as the "20-minute" group, there were actually a number which were terminated at shorter times because of the appearance of unfavorable circulatory signs. The shortest time was 14 minutes. There was no obvious relationship between the duration of exposure to pressure and the degree of fall of the cardiac output.

The results in 13 control animals and 13 experimental animals are described in Table I. We wish to emphasize that the control values were not obtained on the same animals as the experimental ones.

TABLE I

CARDIAC OUTPUTS OF NORMAL DOGS AND DOGS EXPOSED TO POSITIVE PRESS IN SUIT. EXPOSURE 20 MINUTES AT 100 mm Hg

Cardiac Output-Normal (ml. per kilo)	Cardiac Output-During Positive Pressure (ml. per kilo)
220	33
218	110
127	118
179	110
149	161
177	49
168	44
181	85
106	61
171	192
195	51
202	118
156	
Av. 174	Av. 94

b. For 60 minutes--The effects described in the last section were substantially duplicated in six animals exposed to pressure for longer periods (Table II). Five of these animals are exposed to pressure for 60 minutes, one for 40 minutes. The animal which was terminated at 40 minutes appeared to be in circulatory difficulties at that time; its cardiac output was, in fact, lower than that of four of the five other animals, but the value was not completely out of the population; it is therefore included with the others.

TABLE II

CARDIAC OUTPUTS OF DOGS EXPOSED TO POSITIVE PRESSURE IN SUIT.
EXPOSURE 60 MINUTES AT 100 mm Hg

	Cardiac Output-During Positive Pressure (ml. per kilo)
	97
	122
	61
	82
	51
	115
Av.	88

The results at 60 minutes suggest that the adverse circulatory effects of the pressure suit are not the consequence of a progressive process, but depend rather on the initial deviation from the normal situation and are then maintained as a steady state.

2. 200 Millimeters Positive Pressure

Five dogs were exposed to pressures of 200 mm Hg in the suit for periods ranging up to 20 minutes. As in the experiments described previously, the development of circulatory deterioration (as seen in the arterial pressure tracing) was used as the criterion for performing the terminal measurements. The results, which are summarized in Table III, show a reduction in cardiac output of 68 percent of the normal value, considerably greater than the depression at 100 mm Hg.

TABLE III

CARDIAC OUTPUTS OF DOGS EXPOSED TO POSITIVE PRESSURE IN SUIT
EXPOSURE 20 MINUTES AT 200 mm Hg

	Cardiac Outputs-During Positive Pressure (ml. per kilo)
	83*
	63**
	24
	49
	55
Av.	55

*Estimated maximum, necessitated by insufficient sampling (first dog of series).
**Helmet blew off just prior to sampling.

3. Splenectomized Dogs of 100 Millimeters Positive Pressure

In a later section (3-F), it will be shown that almost immediately after the application of pressure in the suit there is a rise of fair magnitude in the hematocrit. It was considered as a possible explanation of some of the effects noted that the increased hematocrit might result in an increase in blood viscosity great enough to reduce the cardiac output to the extent observed.

It was found that the hematocrit rise could be prevented by splenectomy. Proceeding from the hypothesis that the hematocrit rise might be at fault in the cardiovascular abnormalities noted in the suit, a series of splenectomized dogs was prepared. It was presumed that splenectomy might have a protective effect.

The results of these experiments are given in Table IV. It is clear from them that, far from exerting a protective effect, splenectomy is actually deleterious to the animal. It should be noted that in these experiments, the pressure was applied for only 10 minutes, and that the cardiac output reduction was as great as that observed after 60 minute exposure to 200 mm Hg in the intact dog. Further, these animals began from a lower basal cardiac output*.

*The lower basal cardiac output of splenectomized animals is inconsistent with unpublished results of one of us (Ogden, E. and Lukin, L.) and is unexplained.

TABLE IV

CARDIAC OUTPUTS OF SPLENECTOMIZED DOGS EXPOSED TO POSITIVE PRESSURE IN SUIT. EXPOSURE 10 MINUTES AT 100 mm Hg

Cardiac Output-Pre	Cardiac Output-During Pressure
157 ml/kg/min	38
128	70
95	49
167	52
161	102
158	59
104	74
Av. 138	Av. 62

B. THE BEHAVIOR OF THE ARTERIAL PRESSURE

1. 100 Millimeters Positive Pressure

The mean arterial pressure of dogs before inflation of the pressure suit was 118 ± 22 mm Hg. After 20 minutes at 100 mm Hg the pressure fell to 103 ± 24 mm Hg. The individual values of the initial and terminal pressures are given in Table V. This table also shows the terminal pressures in six animals exposed to 100 mm Hg for an hour. As was the case with the cardiac output, there was no evidence of progressive deterioration with time; the change which occurs is fully developed at 20 minutes.

TABLE V

INITIAL AND TERMINAL BLOOD PRESSURES

All values in mm Hg.

20 Min. at 100 mm Hg (12 Dogs)		1 Hour at 100 mm Hg (6 Dogs)		20 Min. at 200 mm Hg (3 Dogs)	
Initial	Terminal	Initial	Terminal	Initial	Terminal
75	56	136	112	109	84
132	140	114	143	130	70
142	122	92	57	126	100
120	94	136	132		
138	131	113	90		
77	84	114	109		
125	95				
120	94				
100	105				
152	135				
136	75				
120	108				
Total 1437	1239	705	643	365	254
Av. 119.8*	103.2	117.5	107.1	121.7	84.7

*Average for all initial pressures, 21 dogs = 119.3 mm Hg.

2. 200 Millimeters Positive Pressure

Twenty minutes of exposure to 200 mm Hg suit pressure results in reduction of the arterial pressure to approximately 75 percent of its initial value. In four dogs this exposure resulted in an average fall to 85 mm Hg. This is consistent with the picture of extensive circulatory deterioration suggested by the major decline which occurred in the cardiac output in the same circumstances.

C. THE DISTRIBUTION OF BLOOD FLOW IN THE ANIMAL IN THE PRESSURE SUIT

1. 100 Millimeters Positive Pressure - 20 Minutes

The blood flow calculation was accomplished as noted in Section II-E. In the case of control animals the values used for cardiac output and regional flow fractions were group averages. In the case of the animals in the pressure suits, each flow was individually calculated from the output of the animal in question and the regional flow fraction of the organ concerned in that animal.

The flow values in control animals are presented in Table VI. All flow values here are adjusted to those for a 10-kg dog by substituting for the cardiac output observed ten times the cardiac output per kilogram in that dog.

In the experimental animals, the flow was similarly adjusted to the value for 10-kg dog.

The following differences between the groups are especially noteworthy.

(1) The flow values in every area are reduced from control values. The reduction in bronchial blood flow is least. Hepatic arterial flow is reasonably well preserved, although it shows a statistically insignificant reduction. The renal blood flow value suffers almost precisely in proportion to the cardiac output. Major flow reductions are seen in the abdominal viscera, the flow reduction ranging from approximately 56 percent (gut) to 88 percent (pancreas). The figures for the adrenal above background were so small in the control animal that no real significance can be attached to them or to the experimental values.

(2) The coronary blood flow is reduced, like that to every other circulatory bed. Surprisingly, the coronary response does not occupy a unique position. The flow is reduced less than that to the abdominal viscera (other than liver), but more than that to the lung and liver.

Several considerations enter into the determination whether coronary blood

flow is reduced excessively in relation to the demands made by the circulation on the heart. True, the coronary circulation is reduced, but so is the work of the heart. At first sight it would appear that the coronary circulation is preserved somewhat better than the cardiac output. Particularly when this is associated with reduction in blood pressure, it would seem quite clear that though coronary circulation is reduced it is not reduced in excess of the work demanded of the heart.

On the other hand, when it is recalled that some of the coronary nutrition is assigned to the maintenance of the integrity of the tissue, rather than to the performance of external work, it is less clear that the coronary circulation is preserved better than the demands upon it. The nutrition supplied for the maintenance of tissue integrity represents a fixed commitment; though overall efficiency may be reduced when the work of the heart is reduced, a different picture may appear when the fixed commitment is recognized and external efficiency calculated on the basis of the ratio of the work load to the nutrition supplied in excess of the fixed commitment. This proposition will be considered in more detail in a later section.

From these results, it is not possible to determine at first glance whether the coronary blood flow reduction is secondary to the reduced load on the heart or is the underlying cause of the reduction in the external performance of the heart. This question will be considered again later.

2. 100 Millimeters Positive
   Pressure - 60 Minutes

The results in the longer experiments showed minor variations from those in the 20-minute experiments. None of them appeared to be of great importance. These results are given in Table VI. The same qualitative statements which were made about the "20 minute" animals are equally valid here.

3. 200 Millimeters Positive
   Pressure - 20 Minutes

It proved impossible to keep animals alive for an hour with the pressure suit inflated to 200 mm Hg. All of the experiments at this pressure were, therefore, terminated after 20 minutes. The results in four such experiments are shown in Table VI.

Granted that the number of animals is too small to warrant a firm conclusion, these experiments appear to indicate an exaggeration of the results at 100 mm Hg. The blood flow in every region is reduced from the control value, just as it was when the suit pressure was maintained at 100 mm Hg. The reduction is greater than previously. In general the reductions are, in individual areas, in accordance with the reduction in cardiac output. Just as the cardiac output is reduced by some 55 percent as the pressure is increased, so too each flow value is of the order of half the 100 mm Hg value when the pressure is elevated to 200 mm Hg.

As noted in a previous section (C-1) the reduction in coronary blood flow appears to be consistent with the reduction in the work of the heart. When it is considered that the heart is doing less work from the standpoint of minute output, it would appear that, all other things remaining equal, the myocardial blood flow should decrease concommitant with the cardiac output. In fact, the blood pressure has fallen, which would appear to justify the expectation of a further decrease in coronary flow. Actually, the myocardial blood flow decreases, but less, not more than the work of the heart. Does this remove from the coronary circulation the onus of responsibility for the circulatory disasters which occur in the pressure suit? This question will be considered in the discussion.

TABLE VI

DISTRIBUTION OF CARDIAC OUTPUT, REGIONAL BLOOD FLOWS AND REGIONAL RESISTANCES OF NORMAL DOGS AND DOGS IN PARTIAL PRESSURE SUITS. (ALL VALUES FOR FLOW AND RESISTANCES ARE ADJUSTED TO 10 K. DOG)

	% CO	Flow (ml/min)	Resistance (dyne sec/cm^5 x 10^{-2})
Controls (10 dogs) Av. C.O. = 1738 ml/min.			
Heart	5.2	96.6	11.5
Kidney	10.9	199.3	5.2
Liver	9.9	154.8	5.4
Lung	4.5	93.8	12.9
Gut	14.0	256.1	3.9
Stomach	2.6	47.1	23.2
Spleen	1.5	27.6	39.9
Pancreas	1.1	21.0	61.7
Adrenal	.04 (2)		
20 Min. at 100 mm Hg (12 dogs) Av. C.O. = 943 ml/min.			
Heart	6.5	60.3	16.2
Kidney	10.7	110.4	7.8
Liver	13.4	121.1	8.0
Lung	9.4	83.6	11.6
Gut	11.7	110.7	9.2
Stomach	1.5	13.0	76.5
Spleen	1.9	16.6	63.6
Pancreas	.34	3.4	397.3
Adrenal	.25	2.1	440.1

TABLE VI. Cont'd

	% CO	Flow (ml/min)	Resistance (dyne sec/cm^5 x 10^{-2})
1 Hour at 100 mm Hg (6 dogs) Av. C.O. = 880 ml/min.			
Heart	5.8	51.6	17.7
Kidney	14.9	122.6	7.5
Liver	13.9	114.7	7.9
Lung	10.1	82.5	11.7
Gut	10.6	97.2	11.1
Stomach	1.4	12.3	85.4
Spleen	1.3	12.3	94.3
Pancreas	.2	2.2	518.4
Adrenal	.3	2.3	440.6
20 Min. at 200 mm Hg (3 dogs) Av. C.O. = 425 ml/min.			
Heart	6.4	24.4	28.1
Kidney	10.7	53.9	17.8
Liver	13.5	60.4	15.0
Lung	9.2	37.5	19.0
Gut	16.7	66.9	10.4
Stomach	1.26	4.9	148.3
Spleen	1.89	5.9	122.6
Pancreas	0.18	00.71	970.0
Adrenal	0.38	1.58	470.4

D. TERRITORIAL VASCULAR RESISTANCES IN THE PRESSURE SUIT

1. 100 Millimeters Positive Pressure - 20 Minutes

The vascular resistances calculated from pressure and flow valves are given in Table VI.

In the dogs exposed to 100 mm Hg for 20 minutes there was an increase in vascular resistance in every area measured except the lung (bronchial circulation). The increase was not a regular one. In the case of the heart, kidneys and liver (hepatic artery) the increase was about 50 percent above the control value. Much larger increases were seen in the vascular resistances of the components of the portal bed (125-900 percent).

2. 100 Millimeters Positive Pressure - 60 Minutes

These animals showed almost the same pattern of territorial resistance

increase as those exposed to the same suit pressure for a shorter time. Again the thoracic organs and kidney showed the smallest resistance increases; the splanchnic had the largest.

3. 200 Millimeters Positive Pressure - 20 Minutes

Only three technically successful experiments were completed in this group. The range of calculated resistance values was considerable, but the direction of the results was consistent.

The increase in territorial resistances noted at the lower suit pressures was maintained or exaggerated, and the lung resistance now became elevated above normal. The myocardial resistance was now elevated to 2.5 times its normal value. The renal vascular resistance rose to 3.5 times its normal value.

The vascular resistance of the gut failed to rise above the values at lower suit pressures, though that of the stomach and spleen showed further increases.

E. CHANGES IN BLOOD IN THE PRESSURE SUIT

As has been noted previously, it was originally intended that the cardiac output be measured in these experiments by use of the hematocrit dilution method[3]. Though we were not successful in applying this method in these studies, we made some observations which suggested that an hitherto unsuspected change was occurring in animals exposed to the suit.

The hematocrit dilution method (conductivity method) for the cardiac output determination depends on the fact that the resistance of whole blood is predictably related to its hematocrit; if a given amount of plasma is injected intravenously as a blood diluent, the resistance of the blood will be reduced in a manner which is explicitly determined by the cardiac output, the measured values of blood resistance before and after the injection, the plasma resistance, and the volume of plasma injected.

In the unsuccessful experiments in which the attempt to determine the cardiac output within the pressure suit was made by this method, it was noted that the resistance of whole blood was greatly increased after the inflation of the suit. This finding suggested that the hematocrit had increased. Since such increases might have been the consequence of either cell increase or plasma decrease, and attempt was made to distinguish between these two by making determinations of the plasma volume. We further made determinations of hematocrit by a more direct method than the electrical one, and of plasma protein concentration.

1. Changes in Plasma Volume

Although the determination of plasma volume by the dye method is ordinarily considered a routine procedure, it is impossible to stress too strongly how large is the margin of uncertainty in making the determination under conditions other than routine.

For example, in ordinary practice, the concentration of plasma label is determined at a fixed time (5 to 30 minutes) after its injection. But it is well-known that most such labels (T-1824, RISA) are extravasated at a significant rate. Clearly, then, the answer obtained will be in error by an amount which increases with both the time chosen for the sampling and the rate at which the material chosen as the label extravasates.

Neither can the procedure of extrapolation of values obtained at two times to zero time be employed without some reservation. The disappearance from plasma of, for example, T-1824, does not, even in its later phases, follow any simple law. Such descriptions as of this late behavior as have been essayed are empirical, and break down badly when they are applied to the early disappearance.

Further, it must be noted that there is, to this moment, lacking any satisfactory explanation of the discrepancy between the blood volume calculated with the aid of labels for the plasma proteins and that determined with labels for the erythrocyte. This discrepancy, which is a large one, has usually been attributed to the existence of capillaries containing blood of low hematocrit; this is said to result from the axial concentration of corpuscular material in capillary vessels. But it has never been made clear why an axial concentation of corpuscular material and a peripheral concentration of plasma should result in a lower over-all concentration of corpuscles rather than the converse. It is sometimes argued that the transit time of the axial stream is less than that of the layers adjacent to the walls. From this it has been deduced that the small vessel hematocrit must be less than that of the large vessels, for any unit of "fast" corpuscular material will associate with more than one unit of the slower fluid in its transit. Granted that this explanation is sound in principle, doubts have been expressed by one of the present authors[11] whether the total intravascular space available for such velocity differences is adequate to account for the discrepancy in distribution volumes routinely observed.

Apart from sophisticated reasons for questioning the significance of the plasma volume measurement, the results of the present experiments revealed a bizarre anomaly, not previously experienced by the writers. This consisted of a secondary rise in concentration of the measuring dye after the completion of the "normal" volume determination. The sample in which this rise was observed was the one used as the blank for the determinations at pressure. Note that if the rise was a spurious one the concentrations of dye taken at pressure should have been diminished by a lesser value; these concentrations would have been greater, and the calculated plasma volume less. But if the rise was genuine and continuous, the samples taken for the volume estimation contained less newly injected dye than they seemed to, and the plasma volume was consequently more.

It may appear over meticulous to emphasize these strictures on the interpretation of the results which are to be described below at this time. Yet the results are, in themselves so bizarre, and so difficult to interpret that we must question the techniques which yielded them before attempting their explanation.

The results which gave rise to the need for these words of caution are given in Table VII. Note that in this table the original data on Evans Blue concentration are given as well as the calculated values for plasma volume.

Bearing in mind the reservations already stated, it would appear that there is a significant reduction in the volume "explored" by Evans Blue after the application of the pressure suit. This volume is, on the average, approximately 170 ml or about 30 percent of the plasma volume. Such a loss in plasma volume, corresponding to a loss in blood volume of approximately 340 ml in a 10-kg dog, would represent a significant hemorrhage; one which was ample in amount to produce the observed effects on arterial pressure and the cardiac output. (The other hemodynamic effects of such a hemorrhage would not, however, be duplicated; this will be discussed a later section).

TABLE VII

PLASMA VOLUME, CELL VOLUME AND BLOOD VOLUME OF DOGS BEFORE AND AFTER 10-MINUTE EXPOSURE TO 100 mm Hg PRESSURE IN SUIT (VALUES REPORTED IN ml.)

Normal Dogs		
	Control (4)	Experimental
Plasma	590	419
Blood	905	824
Cell	316	404
Splenectomized Dogs		
	Control (6)	Experimental
Plasma	602	427
Blood	967	691
Cell	365	264

TABLE VII-a

PROTOCOL OF TYPICAL EXPERIMENT ON PLASMA AND BLOOD VOLUME MEASUREMENTS IN DOGS EXPOSED TO 100 mm Hg IN PARTIAL PRESSURE SUIT

Dog No. 32	Control				
	Blank	E.B 5 min.	E.B. 10 min.	O.D. used in calc. of vol.	Volume = $\frac{\text{O.D. injected mat.}}{\text{O.D. plasma}}$
	.015	.440	.430	.420	620 ml.
	After Suit Inflation				
	.458	1.075	1.058	.608	428 ml.

2. Changes in Plasma Proteins

The increase in Evans Blue concentration observed after the application of the pressure suit was so entirely outside our usual experience that we entertained seriously the possibility that the Evans Blue protein complex was increased in concentration in the plasma as the result of loss of a plasma ultrafiltrate rather than whole plasma from the vascular system. If this were so, it would have been expected that the plasma proteins would increase in concentration upon the application of pressure.

In order to make this determination, we used a direct reading refractometer. Table VIII describes the results.

As the data of this table show, there is a considerable rise in the plasma protein concentration. The rise is large enough to account for the anomalous rise in Evans Blue concentration some time after its injection. Its cause, at the moment, is unknown.

TABLE VIII

PLASMA PROTEINS IN ANIMALS IN PRESSURE SUITS.
(All determinations by refractometer expressed as gm protein/100 ml plasma)

Control	10 Min.	20 Min.	30 Min.
5.0	4.7	5.1	5.2
5.2	5.0	5.9	6.0
5.4	5.4	5.9	6.5
5.8	5.9	6.0	6.9
5.9	6.0	6.1	8.6
6.0	6.0	6.2	
6.0	6.0	6.5	
6.0	6.2	6.8	
6.2	6.4	7.6	
6.2	6.7	7.9	
7.3	7.0		
	7.2		
	7.2		
	7.3		
	7.6		
Av. 5.9	6.3	6.4	6.6

3. Changes in the Hematocrit

At autopsy, these dogs were observed to have exceptionally small spleens, unlike those of otherwise untreated pentobarbitalized animals. This immediately suggested the possibility that many of the cardiovascular disturbances in the experimental conditions were a consequence of splenic discharge of a cell rich blood. Furthermore, as noted in a previous section, we had observed electrical evidence (increased electrical resistance) of increased hematocrit in pressurized dogs. It seemed desirable to check this finding by a more direct technique.

The results of hematocrit determinations before and after the application of pressure are given in Table IX. It will be seen that there was, quite consistently, an increase in hematocrit of some 31 percent after suit inflation. The rise occurred immediately, and showed no evidence of increase with time.

TABLE IX

INITIAL AND FINAL HEMATOCRITS OF DOGS IN PRESSURE SUITS.
(Values expressed as percent red cells)

20 Min. at 100 mm Hg (12 dogs)		1 Hour at 100 mm Hg (6 dogs)		20 Min. at 200 mm Hg (3 dogs)	
Initial	Final	Initial	Final	Initial	Final
33.0*	43.0	36.0	47.0	47.8	67.5
36.0	48.0	35.3	49.9	33.7	45.2
34.7	41.5	41.1	48.7	43.4	61.1
37.0	45.0	35.0	52.2		
39.2	52.9	36.8	55.6		
33.0	42.0		44.2		
33.4	52.4				
38.0	45.6				
37.5	53.9				
45.0	59.0				
30.5	42.1				
39.8	46.5				
Av. 36.4**	47.7	36.8	49.6	41.6	57.9

*Each figure represents the average of at least two and usually three determinations.
**Average for all initial hematocrits (20 dogs) = 37.3%)

a. Changes in hematocrit in the splenectomized dog exposed to pressure--The results described in the last section suggested the possibility that the increase in vascular resistance observed in animals wearing the pressure inflated pressure suit might be a direct consequence of the increased viscosity of the blood. This hypothesis would have attributed a primary role in the genesis of circulatory collapse to malfunction of the spleen.

Seven experiments were therefore carried out in which the cardiovascular changes following inflation of the suit were observed in splenectomized animals. Some of the results have been presented in previous sections. So far as the hematocrit was concerned, splenectomy had the expected effect, i.e., the hematocrit was quite unchanged upon suit inflation. Unfortunately for the hypothesis, however, the animals fared no better, and in fact a good deal worse, than the nonsplenectomized animals in every other significant cardiovascular function. The results on the hematocrit changes are described in table X.

TABLE X

INITIAL AND FINAL HEMATOCRITS OF SPLENECTOMIZED DOGS IN PRESSURE SUITS

	Initial	Final
	43.1	43.7
	39.6	39.1
	32.2	30.1
	49.4	50.2
	39.5	43.2
	26.5	21.4 (Expired)
	43.1	43.6
Av.	39.1	38.8

SECTION IV. DISCUSSION

The problem which these investigations were initiated to elucidate is one of real and practical interest. Dogs wearing inflated pressure suits die or deteriorate badly. Associated with this death or deterioration is a significant failure of cardiovascular function, indicated by diminished cardiac output, fall in blood pressure, and diminished perfusion of blood through a number of vital areas.

Granted that the pressure suits worn by the dogs are not identical with those worn by humans, and granted further that the dogs are anesthetized and the humans are not, the fact that the cardiovascular changes in the dog are so extensive suggests the possibility that there may be some cardiovascular changes in man of similar nature, which while not fatal may be prejudicial to health.

Evidence that this is so is scanty. We are told (personal communication-Donald Rosenbaum) that electrocardiographic changes have been observed in men wearing inflated suits. We are not familiar with any other evidence that cardiovascular function is impaired.

But neither do we know that it is normal. The evidence which is available from the dog experiments is, in fact, all on which we can base our speculations; and this evidence implicates a number of significant abnormalities; all cardiovascular in nature.

A parenthesis is necessary at this point. The fact that the abnormalities observed are cardiovascular in nature may indicate that they are of cardiovascular origin; but it may also indicate that only cardiovascular parameters were investigated. It may not be amiss to use an analogy here; if the proposition were asserted, that ethyl ether in fatal doses killed through its cardiovascular actions, one would have no difficulty in marshalling evidence in favor of the assertion.

It would be easy to demonstrate that the agent reduced blood pressure, exerted a negative ionotropic action on the heart, diminished cardiac output (terminally), etc. But the proposition that ether killed through its cardiovascular actions would remain unproved.

This argument is advanced to indicate that the authors are aware of the possibility that the adverse effects of the pressure suit on the circulation may be a consequence of deleterious changes in some other organ system which are secondarily seen as cardiovascular malfunction. The assumption that circulatory changes are primary introduces a bias into our interpretations of the data. At the present time we are not able to avoid this bias; but we can at least be aware of its existence.

Beginning then with the view that the circulatory changes are primary, we can attribute the cardiovascular changes observed (fall in blood pressure, fall in cardiac output, etc.,) to one of two major causes:

(a) The diminution in cardiac output and the fall in blood pressure results from defective return of blood to the heart as a result of suit induced factors interfering with the normal pressure relationships between the periphery and the heart. In this view, the circulatory disturbances occur in the presence of a normally functioning heart.

(b) The suit induces cardiovascular changes through coronary vasoconstriction, produced by an undisclosed mechanism, and resulting in diminished cardiac performance. In this view, the major circulatory changes which occur in the pressure suit are a consequence of heart failure.

At first sight, it would appear relatively easy to distinguish between these two alternatives. Most simply, this could be done by observing whether the stigmata of heart failure appeared in the animals in circulatory failure in the pressure suit. Unfortunately, in the experimental circumstances evidence of heart failure would be particularly hard to obtain. Elevation of pressure in the great veins, if it occurred, would be difficult to interpret in view of the massive redistributions of pressure throughout the body particularly at the borders of the suit. Pulmonary edema, an almost uniform finding in the experimental animals, might be effected by the external pressure as by condistribution of blood volume as effected by the external pressure as by congestion behind a failing left ventricle. In the same way, volume changes in the chambers of the heart, if they occurred, might be as easily attributed to distortions of static internal pressure relationships acting on the blood as to pathological changes in the myocardium.

Another approach to the problem, and the one which was in fact chosen, was the measurement of coronary blood flow. Briefly put, the argument may be summarized as follows.

If the primary circulatory defect were a peripheral one, that is to say a failure of return of blood to the heart, one would expect to find the characteristic hemodynamic changes of hemorrhage. So far as the myocardium was

concerned this would be expected to be associated with a decrease in the coronary vascular resistance. If, on the other hand, the primary defect were of cardiac origin, the consequence of an abnormal coronary vasoconstriction which resulted in impaired cardiac performance through limitation of the energy sources available to the heart, then an increase in coronary vascular resistance would be expected.

Before presenting this argument in detail, it may be useful to consider some of the evidence which suggests that there are significant changes in the peripheral circulation.

In our earliest experiments, we noted that there was visible edema in those portions of the extremities which were not included within the pressurized parts of the suit. This immediately suggested the possibility that significant fluid losses from the vascular system might be occurring in these parts.

Hematocrit measurement lent support to this hypothesis. The rise in hematocrit was sufficiently large to suggest that a physiologically significant hypovolemia might have developed as a result of extravasation of plasma in the uninclosed portions of the animal. This view received further support from the finding that the Evans Blue space appeared to be reduced in the animals exposed to pressure.

On the other hand, there were some unexplained aspects of these findings that tended to raise some question regarding their significance.

The change which occurred in the hematocrit tended to occur in two phases. The greatest part of the change occurred in the first phase which ordinarily ended within five minutes of the inflation of the suit. The later change, amounting to less than one-third of the original change occurred in the next 15 minutes and in many animals was not seen at all. The group averages for hematocrit at 20 and 60 minutes were the same, suggesting that the process which altered the hematocrit was substantially complete by 20 minutes.

None of this pattern is consistent with the idea of hemoconcentration ocourring through ultrafiltration in the unprotected areas of the body. Such ultrafiltration, according to the studies of Landis[12] and of Pappenheimer[13] would have been slower by at least two orders of magnitude in its earliest phases, would have progressed at a regular rate throughout the experiment and would not have been self limited in the time of observation.

Despite this it would seem probable that fluid losses have occurred from the vascular system. The hematocrit data already cited suggest that there have been substantial losses. Further supporting the idea that fluid losses have taken place are the increased plasma protein concentration (Table VIII)and the reduced T-1824 space (Table VII).

All these, taken together, appear to indicate that a protein-free fluid has been removed from the plasma. It is not necessarily the case that this fluid has been withdrawn from the circulation; quite conceivably it may have entered the red cells. Such a shift of fluid from plasma to cells would account for the rise in hematocrit as well as the fall in Evans Blue space and

the rise in plasma proteins. It would also account for the fact that the reduction in blood volume is quite insignificant compared to the loss in plasma volume. On the other hand, it is very difficult to see why splenectomy should prevent this shift. (The splenectomized dog shows equal reduction in blood and plasma volume, no change in plasma proteins and no change in hematocrit after inflation of the pressure suit). Neither is any mechanism apparent which could account for such a shift of fluid.

Although we are unable at this time to account for the missing fluid, it should be noted that the total diminution in blood volume is not impressively large. Although the reduction in plasma volume is more than 30 percent, the reduction in blood volume is only some 8 percent. Ordinarily, it would not be expected that so small a reduction in blood volume would produce any major effect on the cardiac output, such as that seen in these experiments.

Even granting that the coupling of a slight decrease in blood volume with an increase in blood viscosity (resulting from the increased plasma protein concentration and hematocrit) might result in less effective venous return and a reduction in cardiac output of the magnitude observed, we must pose the question: Are the hemodynamic changes characteristic of insufficient cardiac output actually observed in the experimental animals?

Insofar as the peripheral circulation in hemorrhage and shock can be taken as representative of the condition of decreased cardiac output due to failure of venous return, the answer to this question must be in the negative.

Concentrating attention on the coronary circulation, there is a wealth of evidence to indicate that coronary vasodilation is the characteristic response to diminution in cardiac output and arterial pressure. Most of this evidence is reviewed by Wiggers[14], and some of the more recent information on the subject is summarized by Sapirstein, Bredemeyer and Sapirstein[15]. Without exception, all who have studied the coronary circulation in conditions of diminished cardiac output have found its resistance to be decreased.

This may in itself be considered strong presumptive evidence that the circulatory defect in the pressure suit is of cardiac rather than peripheral origin. Yet it may be argued that the coronary vasodilation of the hemorrhaged animal is a consequence of a change in blood volume rather than of a change in minute output. If this were so, the argument that coronary resistance is increased in the present circumstances where blood volume is preserved reasonably well while the cardiac output falls would lose much force.

The question may be viewed from another aspect. Unless some external influence were at work upon the coronary circulation, it would seem reasonable to assume that the coronary blood flow should vary directly with the metabolic needs of the heart. If this proposition is true, it would be anticipated that reduction in the myocardial metabolic requirement should be associated with a proportional reduction in the coronary blood flow. If, in a given set of circumstances, it were found that coronary blood flow was more grossly impaired than the metabolic requirement of the heart was reduced while the coronary vascular resistance was above its minimal level, it would seem justifiable to assume that a coronary vasoconstrictor effect was being displayed.

On cursory examination, the data on coronary blood flow and myocardial work presented in the present experiments seem to indicate that if anything the coronary blood flow is less reduced than is the work load on the heart. Thus, in the control animals, the work of the heart was 2.8×10^8 ergs/min.; coronary blood flow was 96.6 ml/min. In animals exposed to 100 mm Hg for 20 minutes, the work of the heart was reduced to 1.3×10^8 ergs/min., a reduction of over 50 percent. The coronary blood flow was reduced about 38 percent. Upon exposure to 100 mm Hg for 60 minutes the work of the heart fell to 1.25×10^8 ergs/min., (45 percent of normal) while the coronary blood flow was 53 percent of normal. In the three technically successful experiments in which pressures of 200 mm Hg were maintained for 20 minutes, the work of the heart averaged 0.5×10^8 ergs/min., about 17 percent of normal; the coronary blood flow was 26 percent of normal. Thus in each of the circumstances studied, it would appear that the coronary blood flow is reduced less than the work of the heart.

However, in these calculations, we have neglected the fact that the myocardial blood supply has two commitments. Not only must it supply the oxygen and nutrients that permit the heart to perform external work but it must also provide a fixed commitment of energy sources for the maintenance of the tissue. Although estimates of this commitment are, at best, approximations, it seems probable that it is of the order of 20 percent of the basal work of the heart in these experiments approximately 0.6×10^8 ergs/min. If we accept this as a reasonable figure, then the total energy commitment versus the available blood flow in the circumstances described above presents a radically different appearance. In the normal heart each ml of blood flow supports 3.5×10^6 ergs of work. In the animal inflated at 100 mm Hg for 20 minutes, the same value is 3.2×10^6. In the longer exposure to 100 mm Hg, the corresponding value is 3.6×10^6. The relative constancy of the energy calculated to be obtained from 1 ml blood over a two fold range of flow tends to support the assumptions upon which the calculation is based. When the same calculation is performed upon the data obtained at pressures of 200 mm Hg., it is found that each ml of coronary blood flow must support 4.5×10^6 ergs of work. It seems probable that in normal circumstances such a demand would result in a lowering of oxygen tension within the myocardium and a consequent vasodilation until the normal ratio between work requirement and blood flow was restored. The fact that this is not observed here (coronary resistance is actually increased) must be considered presumptive evidence that the normal mechanism which couples coronary blood flow and myocardial energy requirements has been overridden by some coronary vasoconstrictor effect by improvement in cardiac efficiency.

The speculative nature of the argument outlined above is readily apparent. Not only is it explicitly assumed that the basal requirement of energy for myocardial maintenance is constant, but also it is tacitly assumed that the ionotropic environment of the heart remains constant, that myocardial extraction of oxygen is constant, and that the efficiency of the coupling between chemical and mechanical energy of the heart is unchanged in the experimental circumstances. Granted that all these assumptions are made, the fact that the conclusion to be drawn from them is the same as that drawn from the fact that the myocardial resistance is not diminished in the presence of diminished cardiac output and blood pressure, unlike the situation in hemorrhage, tends to strengthen confidence in both arguments. Using either argument, the expected result would have been coronary vasodilation, if a peripheral circulatory failure were the

determining factor; the fact that coronary vasoconstriction is found tends to point the finger of suspicion at a coronary vasoconstrictor mechanism as being the prime mover in the circulatory difficulties found in the pressure suit.

Assuming for the moment the correctness of this conclusion, several possible coronary vasoconstrictor circumstances which may develop in the pressure suit come to mind:

(1) The fact that the pressure suit is inflated with pure oxygen and that the arterial blood is thus at a partial pressure of 860-960 mm Hg with respect to oxygen may result in coronary vasoconstriction. It is conceivable that the higher partial pressure in the arterial blood, though it represents little additional blood oxygen content, may speak more loudly to the coronary vessels than the relative ischemia of the tissue, which may have had its blood supply reduced as a consequence of an apparent surfeit of oxygen in its incoming blood.

(2) There seems to be no doubt that the pressure suit produces, directly or indirectly, a considerable shift in the normal patterns of blood flow distribution. Of these, the one most strikingly displayed in the present experiments is a relative increase in the arterial perfusion of the liver, and a decrease in the portal perfusion. One may imagine the possibility that coronary vasoconstrictor substances are produced when blood passes through the hepatic arterial circuit, while coronary vasodilators are engendered when blood takes the portal route. A shift in the proportions of blood distribution might well, if this were the case, result in coronary vasoconstriction or coronary vasodilation on a humoral basis. Note that this is not presented as a possibility to be seriously entertained in its present form; but it may serve as an example of the type of disturbance which may occur in the animal exposed to a nonuniformly distributed pressure which may increase or decrease the resistance of vascular beds selectively.

(3) What may be an important clue to the nature of the disturbance is offered by Rosenbaum's[16] observation that many of the adverse circulatory effects observed in pressure suits are prevented by atropine. It has been suggested as a possible mechanism for this effect that the circulatory effects are brought about by acetylcholine discharged in response to the increased volume (or pressure) of blood in the low pressure vessels of the chest. Admittedly, this interpretation is a highly speculative one, there is, however, considerable evidence to support the idea that there is a volume sensing mechanism in the low pressure blood vessels of the thorax; and there is also evidence to indicate that intrathoracic volume relationships are distorted upon the application

of the pressure suit[1]. It is less clear that acetyl choline is the agent which mediates the response of the volume receptor; nor is it at all clear that the primary action of acetylcholine in such a volume regulatory system is on the myocardial circulation. Nevertheless the subject appears to warrant further investigation.

SECTION V. SUMMARY AND CONCLUSIONS

1. Dogs placed in bladder-type partial pressure suits show important circulatory changes. Chief among these are a considerable fall in the cardiac output and a moderate fall in the arterial pressure.

2. Changes in the cardiovascular system occur during the first 20 minutes, and there is no evidence of further progressive deterioration with time.

3. These experiments were begun in an attempt to determine whether the circulatory changes depended upon a reduction in coronary blood flow secondary to increased coronary resistance.

4. Coronary blood flow was measured by the indicator fractionation technique. It was found to be reduced in the bladder-type partial pressure suit. Coronary resistance, measured as the ratio between arterial pressure and coronary blood flow, was found to be increased in dogs wearing the bladder-type partial pressure suits.

5. The fall in coronary blood flow and the rise in coronary resistance may have been primary, or they may have been a secondary effect of the diminution of the work on the heart brought about through peripheral circulatory changes in the pressure suit. Arguments are advanced to indicate the probability that the coronary changes are primary rather than secondary. These are based on (1) the dissimilarity between the coronary blood flow changes in the pressure suit and those observed in animals where the return of blood to the heart is impaired by hemorrhage and (2) the unfavorable energy demand/blood flow relationship which develops in the pressure suit in certain circumstances without compensatory coronary vasodilation. These considerations make it seem very likely but not entirely beyond question that a true coronary "insufficiency" is the cause of the other effects observed.

6. Some examples of possible types of explanations of an overriding coronary vasoconstriction in the pressure suit are given. They include the possibility that a high partial pressure of oxygen in the arterial blood may predominate over a low partial pressure of oxygen in the tissues in determining regional blood flow; the possibility that altered perfusion of organs releasing coronary vasoconstrictors or vasodilators may modify the relative proportions of each reaching the coronary circulation; and the possibility that abnormal volume displacements cause through a volume receptor system, discharge of acetyl choline which exerts a coronary vasoconstrictor effect.

BIBLIOGRAPHY

1. Williams, Jack and Horvath, Steven M. Pulmonary Blood Volume and Circulatory Alterations in Dogs Exposed to Compensated High Intrapolmonary Pressures. WADC Technical Report 58-471, April 1959.

2. Hitchcock, Fred A., Reininger, E. J., and Carter, Earl. Cardiovascular Effects of a Pressure Suit on a Dog. WADC TR 57-700, Contract AF33(616)-3825 between The Ohio State University Research Foundation and Wright Air Development Center, December 1957.

3. Goodwin, R. S. and Sapirstein, L. A. Determination of Cardiac Output by a Hematocrit Dilution Method Employing Autogenous Plasma. Circulation Research 5, 531, 1957.

4. Rothe, C. F. and Sapirstein, L. A. A Rapid Blood Sample Collector for Use in the Determination of the Cardiac Output. Am. Heart J. 48, 141, (1954).

5. Kety, S. S. and Schmidt, C. F. The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man. Theory, Procedure and Normal Values. J. Clin. Invest. 27, 476, (1948).

6. Sapirstein, L. A. Fractionation of the Cardiac Output of Rats with Isotopic Potassium. Circulation Research 4, 689, (1956).

7. Sapirstein, L. A. Regional Blood Flow by Fractional Distribution of Indicators. Am. J. Physiol. 161, 193,(1958).

8. Sapirstein, L. A. and Hanusek, G. Cerebral Blood Flow in the Rat. Am. J. Physiol. 193, 272,(1958).

9. Sapirstein, L. A. and Mandel, M. J. Blood Flow in the Aortic Wall. Circulation Research 8, 135, (1960).

10. Sapirstein, L. A. Organ Localization of Intravenously and Intra-Arterially Injected Microspheres in Rats: Circulation Research. (In Press)

11. Sapirstein, L. A. Passage of Macromolecules Across Capillary Walls. In "Symposium on Factors Influencing Exchange of Substances Across Capillary Walls." Published in Microcirculation, Proceedings of the Fifth Conference on Microcirculatory Physiology and Pathology, University of Illinois Press (1959).

12. Landis, E. M. Capillary Pressure and Capillary Permeability. Physiological Reviews 14, 404, (1934).

13. Pappenheimer, J. R. Passage of Molecules Through Capillary Walls. Physiological Reviews 33, 387, (1953).

14. Wiggers, C. J. The Physiology of Shock. Commonwealth Fund, New York, 1950.

15. Sapirstein, L. A., Bredemeyer, A. and Sapirstein, E. Effect of Hemorrhage on Cardiac Output and Its Distribution in the Albino Rat. Circulation Research 8, 135, (1960).

16. Rosenbaum, D. Survival Studies at High Altitudes: Animal Experimentation. Technical Note WCRD 55-3, January 1955.

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